BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

MAY, 1943

MULTIPLE SCLEROSIS AND "ENCEPHALOMYELITIS"*

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HISTORICAL

ABOUT a century ago, in 1836 or 37,[1] Sir Robert Carswell, Professor of Pathology at the University of London, published an installment of his handsome atlas of pathology[2] containing a picture and description of a most interesting neurologic specimen. The pons and cord were spotted with greyish areas of atrophy of irregular shape, and in the lumbar region was an area of softening. No history was available.

Within a year or two, the great French pathologist, Cruveilhier, described three similar specimens in his own atlas of pathology,[3] also coming out in installments. His description was far more complete than Carswell's and in addition, he was able to supply two typical case histories.

During the following twenty years, there were sporadic anatomical and clinical studies of the various types of degeneration of the spinal

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cord. An example is a clearly written pathologic report by a young Philadelphian, Dr. S. Weir Mitchell. But little progress was made toward a practical working knowledge of this peculiar disease, until the publication in 1868 of a clear, concise review of the literature and description of original cases by Jean Marie Charcot.[4] He definitely fixed the name of the disease—"Sclérose en plaques disseminée"—and gave a succinct account of the pathologic changes, which is in certain ways better than the descriptions in some modern textbooks. He emphasized the haphazard distribution of the lesions, their sharp outlines, the breakdown of myelin sheaths, the preservation of a variable proportion of axis cylinders, the glial scar, and the thickening and obstruction of vessels.

His description of the clinical picture was clear, though oversimplified. It was based on the illness of a servant girl in his own household, who finally came to autopsy at the Salpêtrière. Her symptoms—nystagmus, intention tremor and scanning speech—constitute the triad familiar to every medical student. In a later work (1879), Charcot[5] went further, and called attention to the milder cases, which we now recognize as the commonest type.

Charcot's lectures on neurology became known all over the world, and doubtless as a result, a steadily increasing number of cases of multiple sclerosis began to be reported. In the last century, it was considered to be a rare disease, but modern statistics show it to be a common one, especially if we include its acute forms, usually known as encephalomyelitis, acute transverse myelitis and optic neuritis.

Prevalence of multiple sclerosis and related disorders: Owing to variations in standards of diagnosis and in local prevalence, it is extremely difficult to estimate the incidence of multiple sclerosis. A survey in Switzerland showed 7 per 10,000 in certain localities.[6] In recruits examined for the last war, the incidence was about 1 per 10,000 (including rejections and discharges). The last figures for selectees in the New York City area showed a rate of rejection of about 6 per 10,000 for multiple sclerosis, encephalitis and myelitis. These figures are probably all on the low side, for recent experience shows that the diagnosis is more often missed than erroneously made. With the use of modern refinements in diagnosis, multiple sclerosis and encephalitis need no longer be "wastebasket" categories.[7] It is clear that in this locality at least, multiple sclerosis is by no means a rare disease.

There is a pronounced difference in the *local* incidence of multiple sclerosis. It is common in the Baltic countries, Scotland, the North Atlantic seaboard and the Great Lakes region. It is rare in the Mediterranean countries and our own South, and almost unknown in China, Turkey, India and Japan.

Scope of the category of demyelinating diseases: Multiple sclerosis as ordinarily defined, is characterized pathologically by the existence of glial scars scattered throughout the nervous system. There is now practically complete agreement among neuropathologists that the gliosis is secondary to tissue damage, and that each lesion goes through an acute stage (Marburg[8]). It is usually agreed that the acute lesions are marked by edema and local glial proliferation and perivascular infiltration.

Beyond this point, there are many differences of opinion, and here I can do no more than express my own. I believe, with Marburg,[8] Ferraro,[9] Juba[10] and a few others, that the disorders characterized by scars interspersed with acute lesions are but the chronic relapsing form of the acute demyelinating diseases (Figures 1, 2). This group of diseases includes the type known as post-infectious and disseminated encephalomyelitis, Schilder's disease, diffuse sclerosis, neuromyelitis optica, acute transverse myelitis, and "idiopathic" optic and retrobulbar neuritis.[11] The histopathology of these disorders is fundamentally uniform;[9,10,11,12] the differences are in location and intensity of the lesions Naturally, an acute transverse lesion of the cord is more apt to be fatal than one in the optic nerve; naturally also, massive lesions of both hemispheres (Schilder's disease, diffuse sclerosis) is more devastating than small isolated plaques, but the type and varieties of tissue reaction are the same. The acute disorders comprise the great majority of the cases of "encephalitis" encountered in practice; the specific encephalitides, due to known infective viruses, present a wholly different aspect, pathologic and clinical, and are at present rare in this region.

Since there is no agreement whatever among neuropathologists as to the etiology of these disorders, I shall postpone consideration of it until after a sketch of their clinical manifestations, which should be taken into account in deciding among rival theories.

Predisposing factors—Infections: Taking the demyelinating diseases as a group, it is clear that a sudden or subacute onset is common and often apparently precipitated by exogenous factors. This is most clearly

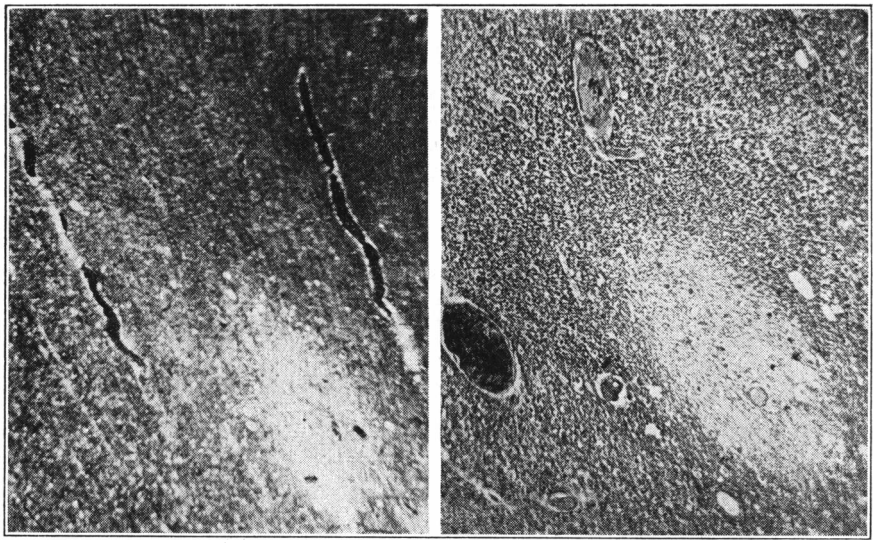

Fig. 1 Fig. 2

Fig. 1—Multiple sclerosis. A small, early lesion, consisting of loss of myelin, damage to axis cylinders, and glial proliferation. Note the tortuosity and engorgement of the veins draining the area. Mallory's connective tissue stain.

Fig. 2—Postvaccinal "encephalitis." Early demyelinating lesion. Note the similarities to Figure 1. The thrombosis of the neighboring vessels is obvious. Mallory's connective tissue stain.

seen in the post-infectious "encephalomyelitides." In the post-vaccinal form, the onset of the "encephalitis" coincides with the height of immunity in most cases; that is, it occurs on the 11th day in most cases.[13] In post-measles "encephalitis," the onset of cerebral symptoms usually occurs in five days from the outbreak of the rash. While these two types of post-infectious "encephalitis" are the most widely recognized, they are not the most common. Actually, the banal infections of the respiratory tract—pneumonia, sinusitis, tonsillitis—are more often the apparent precipitating cause of optic neuritis, "encephalomyelitis," acute transverse myelitis, neuromyelitis optica, and multiple sclerosis, than are any of the specific infectious diseases.[14]

Examples should be familiar to all practitioners. An instance is the following:

J. M., a previously healthy medical student, developed a paronychia of the middle finger of the left hand in 1927. Three days later, he came down with a quadriplegia and symptoms of bulbar disease, and had to be tube-fed. There was an increase of

cells in the spinal fluid. A diagnosis of "encephalitis" was made. After a convalescence of several months, he considered himself entirely well and returned to work. Following a period of fatigue, he developed a paronychia on the other hand, and had a recurrence of the same symptoms. He recovered from this also, but with a residual limp and hemiataxia. He graduated from medical school and went into practice. Every year or so, he has an attack of sinusitis, and his weakness and ataxia reappear. Each attack leaves him slightly worse, and sometimes adds a new symptom, but he is still able to practice.

Syphilis should probably be included among predisposing infections. The incidence of serologic evidences of syphilis is slightly higher among patients suffering from multiple sclerosis, than in the population at large.

Trauma: Acute traumatic "encephalomyelitis" is a recognized disease entity, but it is relatively rare. Adler[14] found two cases, compared with thirty following infections. The influence of injury is apparent in many cases of multiple sclerosis, however. Some striking examples are the following:

The R. sisters were identical twins, aged 27, who earned their living by tap-dancing at night clubs. Shortly after finishing an engagement, one of them slipped and fell, landing on her buttocks. She was certain that she felt perfectly steady and normal up to the time of the fall; but at once she felt a weakness of the legs, and a numbness up to the nipples. She had to be helped home. A neurologist was called, and found bilaterally positive Babinski signs. From that on, she ran an intermittent downhill course, finally presenting an unmistakable picture of advanced multiple sclerosis. The other twin remains in good health.

A female schoolteacher of 28 was brushed by a passing automobile and thrown down, but was not unconscious. She was unable to rise, and had to be taken to the hospital. There she was found to have a mild paraplegia, intention tremor and nystagmus. She had been incapacitated for three months when last seen.

Pregnancy and Menstruation: A fatal "encephalomyelitis" is apparently rare in pregnancy, but few women who have had retrobulbar neuritis or other manifestations of multiple sclerosis can pass through pregnancy and the puerperium without danger of an exacerbation.[15] Initiation or exacerbation of multiple sclerosis occurred in 60 per cent of Beck's female patients[16] who had borne children, and this corresponds with my own experience. Similarly, menstruation has an adverse effect, particularly in the terminal stages of the disease.

Thus, one woman (in whom the diagnosis was confirmed at autopsy) began to have irregular periods toward the end of her course. Preceding each one she would have a two days' fever, and become completely paralyzed, often unconscious. Each of these events marked a step downward in the progress of her disease, which was practically stationary between them.

Toxic Substances: "Encephalomyelitis," "myelitis" and multiple sclerosis are not infrequently precipitated by the administration of sera, vaccines, and certain chemicals. In a case in my collection, an acute paraplegia followed the day after a vaccination against typhoid fever

and similar cases are reported in the literature.[17] The incidence of "encephalomyelitis" during the Pasteur treatment against rabies is about .04 per cent (Wilson[18]). Tetanus antitoxin[19] (and experimentally tetanus toxin[20]) have also apparently been responsible for the onset of multiple sclerosis. I have seen two cases in which relapses followed immediately upon administration of histamine. Perhaps the case of "encephalitis" following a burn, reported by Globus and Bender[21] belongs in this category also. In animals, coagulants produce a similar picture.[22]

Of inorganic substances, the injection of sulfanilamide has been followed by a typical "encephalomyelitis."[23] Carbon monoxide poisoning has precipitated a progressive multiple sclerosis.[24] Experimentally, repeated administration of potassium cyanide rather regularly brings about the characteristic pathologic changes.[25] Lead poisoning has been found in multiple sclerosis,[26] and excessive amounts of arsenic in cases of "encephalomyelitis."[27] Finally, the typical "hemorrhagic encephalitis" produced by arsphenamine, and some of the cases of carbon monoxide and nitrous oxide poisoning, closely resemble post-infectious "encephalomyelitis."

Other Factors: Over-exertion, chilling, fright and emotion are often mentioned as precipitating causes of multiple sclerosis, and von Hoesslin[28] gives some rather low figures of incidence. In the category of emotion (rather than of trauma) might go the cases in which lumbar puncture or venipuncture have apparently brought on exacerbations of an established multiple sclerosis. This I have seen.

Brickner and Brill[29] have cited cases in which dietary indiscretions or the use of a greatly restricted diet have been followed by relapses. This I have not happened to observe. The possible influence of diet will be considered under etiology.

Manifestations: There is no single syndrome that can be considered typical of multiple sclerosis and the demyelinating diseases. A great variety of symptoms may occur: Weakness or numbness of one or more extremities, tremor, ataxia, nystagmus, speech disturbances, emotional lability, retrobulbar neuritis or papillitis, with central scotoma, diplopia, disturbances of bladder function and the "electric phenomenon" are frequently found in both the acute and the chronic stages of the disease. Less well recognized are various psychoses,[30] convulsions,[31] decrease in potency, papillitis, symptomatic paralysis agitans,[32] trigeminal neuralgia,[33] sciatica and other neuritic pains, headache, mus-

cular atrophy,[34] oscillopsia,[35] drowsiness, difficulty in swallowing, hemianopia, and aphasia. An outstanding review of the manifestations of multiple sclerosis may be found in Marburg's monograph.[36]

In the acute, fulminating cases of "encephalomyelitis," fever, headache, convulsions, coma, stiffness of the neck, hemiplegia, oculomotor palsies, and acute optic neuritis are common (Adler[37]).

The course of symptoms is often characteristic. They sometimes come on within a few minutes, or overnight. A patient may watch a scotoma develop, or be thrown down by a hemiplegia. Often, the onset is subacute, gradually increasing over days, sometimes with fever and leukocytosis. Even when symptoms come on insidiously, the patient is able to remember slight variations in progression. Once at their height, symptoms tend to improve or disappear. If relapses occur, they more often consist of an exacerbation of existing symptoms, than of the appearance of new ones, though both may concur.

A single isolated "signal symptom," such as numbness of one extremity, diplopia, or central scotoma, may appear and disappear long before the disease as a whole becomes recognized.

In analysis of symptoms and signs, the important points for diagnosis are *evidence of lesions scattered in time and space.* Most of the lesions affect white matter, so that signs of injury to the cortico-spinal, cerebellar and vestibular systems are common. The lesions are rarely complete over large areas, so that gross sensory defects are unusual (except in acute stages). Paraplegia with a sensory level is not rare, usually as a terminal event. Grey matter suffers less than white matter, so that convulsions, muscle atrophies, and nuclear palsies are unusual; but the more fulminating the onset, the less the lesions respect nerve cells.

Examination of the spinal fluid is of great help in diagnosis. In multiple sclerosis according to Merritt,[38] the cells are increased beyond 5 in 28 per cent of cases, but rarely over 100. Protein is increased in 24 per cent of cases. Abnormal gold sol curves are found in 71 per cent of cases. A slight increase of pressure is occasionally recorded. In only 17 per cent of cases is the fluid entirely normal. Naturally, examination of the spinal fluid is of great help in ruling out syphilis and tumor.

A somewhat different picture is found in fulminating cases of "encephalomyelitis." The cell count is usually higher, and may reach 8,000. Pressure is occasionally elevated. The protein is rarely much elevated, and a frankly positive gold sol curve is practically never found.

TABLE I

PRINCIPAL SYMPTOMS IN 133 CASES OF MULTIPLE SCLEROSIS

	AS FIRST SYMPTOM		AS SUBSEQUENT SYMPTOM	
	Total	*Improved*	*Total*	*Improved*
Paraplegia	19	9	70	22
Ataxia; tremor	23	10	44	15
Monoplegia	24	13	33	18
Scotoma	20	16	32	20
Numbness of one extremity	20	15	26	13
Bladder symptoms	6	4	39	15
Diplopia	18	12	24	14
Numbness of both legs	7	5	19	15
Disturbance of speech	2	2	22	4
Mental deterioration	2	0	16	1
Hemiparesis	6	3	11	5
Pain (radicular)	1	0	13	5
Hemianesthesia	5	4	4	4

If the patient survives this acute phase, the spinal fluid picture gradually becomes that typical of multiple sclerosis.[12]

Spinal punctures (and other procedures such as encephalography or even venipuncture) are sometimes followed by exacerbations—doubtless a non-specific effect.

Visual fields should be plotted in every suspected case. The presence of a central or ceco-central scotoma, even relative, is characteristic.

Electroencephalography is sometimes useful. In cases in which only paraplegia or ataxia are evident, a cerebral focus may be revealed. Fluctuations in the extent of an area of phase reversal may be the clearest manifestation of the typical remissions and exacerbations.

A cystometrogram often furnishes additional objective evidence of a lesion of the cord.

Psychometric studies are helpful in assessing prognosis and ability to work. The record of achievement is usually spotty and variable.

Course and Prognosis: The diagnosis of multiple sclerosis is usually

considered to be worse than a sentence of death. Thus, Osler's textbook states that "ultimately, the patient, if not carried off by some intercurrent infection, becomes bedridden." Certainly all of us have seen patients in the late stage of the disease, helpless and miserable, yet clinging to life often for a decade or two.

On the other hand, a survey of a large series of cases shows that remissions are common, and substantial spontaneous recovery is not rare. Von Hoesslin[28] found 17 per cent of remissions among his 516 cases, lasting for periods up to forty-five years. Dr. Brown and I reviewed 133 cases which we had personally observed,[7] and found that some improvement occurred at some time in ninety-two of them. Twenty per cent were working, 47 per cent were ambulatory, 15 per cent were helpless, and 12 per cent were dead. It was clear, moreover, that certain symptoms carried in themselves a better prognosis than others. Data for the more common symptoms are given in Table I.[7]

The following conclusions resulted from the detailed study.

1. The prognosis is better for early symptoms than for late ones—hence, of course, the transient character of the "signal symptoms."

2. Symptoms evidently due to small lesions, such as diplopia, central scotoma or sensory disturbances of one extremity, tend to regress within a few months, while symptoms due to larger lesions such as paraplegia, ataxia and mental deterioration are usually permanent.

3. Isolated symptoms disappear in a far higher proportion of cases than do the same symptoms occurring in conjunction with others (usually therefore due to large lesions).

4. Symptoms tend to grow more severe as the disease progresses.

5. Cases in which severe symptoms occur at the outset, usually run a much more malignant course than those in which the early symptoms are mild and transient. There are, however, many exceptions to this rule.

6. Cases seen in office practice tend to do much better than those seen on hospital wards. Periods of improvement were found in 87 per cent of the former and in only 62 per cent of the latter.[7] Whether this is because ward patients have more severe symptoms at the outset, or whether it is due to differences in economic level, the fact is undoubted.

While the survey did not bring out the point clearly, it is widely believed by neurologists that the course of the demyelinating diseases is more stormy ("encephalitic") in children, more gradual in middle

life. An onset after 40 is somewhat unusual, but may occur.

Etiology and Mechanism of the Disorder: All the information we can muster is still too scanty to give a complete picture of the pathogenesis of multiple sclerosis and the "encephalitides."

Some general possibilities can at once be ruled out. It is not primarily a hereditary disease. Thums[39] has traced 14 pairs of identical twins, of which one had multiple sclerosis; in no instance was the other affected. (This paper adds a 15th pair). There are, to be sure, occasional instances in which two cases have occurred in the same family, but they are probably to be ascribed either to coincidence, or to confusion with hereditary ataxia which sometimes closely simulates multiple sclerosis.

Multiple sclerosis and the related disorders are not deficiency diseases. They are rarest where dietary deficiencies are most prevalent—namely, in China and our own Southern states. Attempts at treatment with high vitamin diets and injections of liver extract were begun fourteen years ago at the Boston City Hospital, and were abandoned when it became clear that the course of the disease was unaffected.[40] More recently, intensive treatment with a wider variety of vitamins (including vitamin E) at the Neurological Institute has yielded equally negative results.

It is extremely unlikely that multiple sclerosis and the demyelinating "encephalitides" are due to a living virus. The pathologic changes are entirely distinct from those resulting from known specific infections; for example, poliomyelitis and equine encephalitis.[41] Although countless attempts have been made to transmit the disease to animals, by many bacteriologists including Noguchi, all have been negative; not a single one of Koch's postulates have been fulfilled. The presence of spirochetes in the lesions has been occasionally reported, but competent observers have failed to corroborate the observation.[42] Schaltenbrand's recent brief note,[43] reporting production of a disease in animals not resembling multiple sclerosis, is unsatisfactory in many respects.

Meanwhile, some positive evidences indicating an entirely different type of etiology have gradually accumulated.[44,45] Lesions closely resembling those of "encephalomyelitis" in the acute stage, and those of multiple sclerosis in the chronic stage, have been produced by obstruction of cerebral venules.[45] Similar lesions may be brought about by injection of coagulants[22] or of asphyxial poisons.[25] Thrombi are found regularly in acute lesions, both of "encephalomyelitis" and of

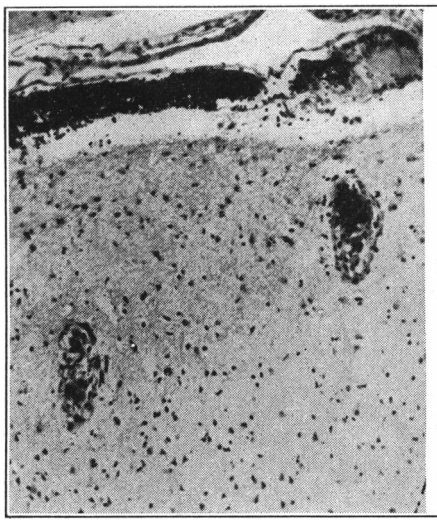

Fig. 3

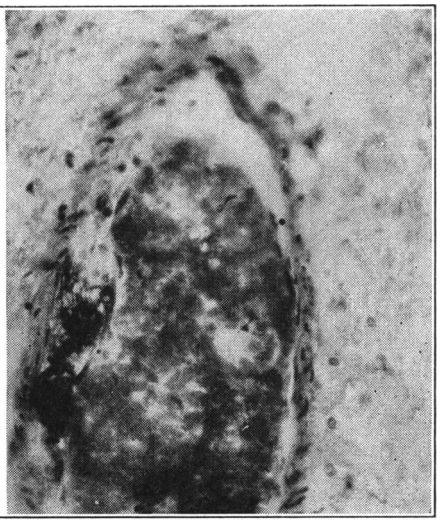

Fig. 4

Fig. 3—Multiple sclerosis, with death in an acute exacerbation. Two small thrombosed veins draining a plaque. Mallory's connective tissue stain.

Fig. 4—Multiple sclerosis. Fresh thrombus in a vein adjacent to a plaque. Mallory's connective tissue stain.

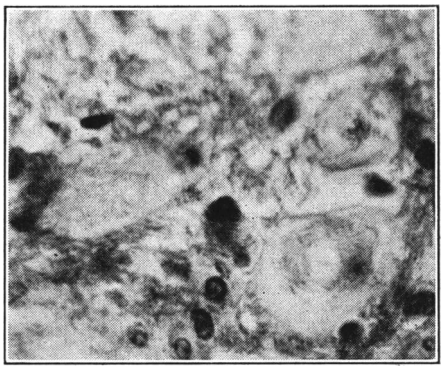

Fig. 5—Multiple sclerosis. Fibrous cords representing the remnants of obstructed vessels, adjacent to the lateral ventricle. Mallory's connective tissue stain.

multiple sclerosis (Figures 3, 4, 5) and in other organs of the body.[44] There is a peculiar lability of the clotting mechanism in cases of multiple sclerosis.[46,47]

All these facts may be fitted together in some such theory as the following: There are individuals who suffer from a peculiar lability of the clotting mechanism of the blood. Whether this is congenital or acquired is not clear. If it exists, however, any slight disturbance of

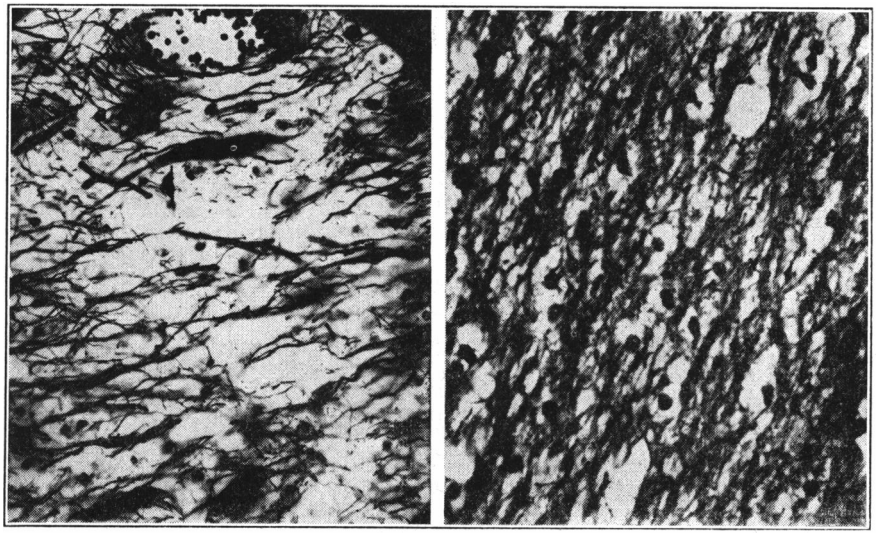

Fig. 6—Multiple sclerosis. Axis cylinders within a plaque (left), and in relatively normal adjacent tissue (right).

the equilibrium of the body may precipitate a shower of minute thrombi in various tissues. Most of these cause no permanent damage, but any that occur in the brain leave a permanent landmark behind and a local vascular abnormality which predisposes to further clotting. If the process is sufficiently stormy, a widespread destruction is produced, and the patient dies with the manifestations of "encephalomyelitis." Limitations of space forbid going into further details, but they may be found in some of the references already cited.

Treatment: A study of the lesions of multiple sclerosis makes it clear that a large proportion of axis cylinders are destroyed in the acute phase of the process[48] (Figure 6). The larger the lesion, and the longer the disease has continued, the more severe the damage to axons. A useful regeneration of axis cylinders in the central nervous system is at present inconceivable. It follows, therefore, that no treatment (beyond ordinary regulation of hygiene) can be expected to influence the course of lesions which have already occurred.

This conclusion is borne out by a statistical study of the effects of the various forms of treatment now in use.[40] The average rate of improvement closely approximates that found in untreated cases.

These facts, and the theory of pathogenesis just outlined, do not necessarily mean that all attempts at treatment are hopeless. They do, however, imply, *that a given treatment should be judged not on the basis of its effect on existing symptoms, but on its success in preventing relapses.* If exacerbations can be definitely prevented, the normal tendency is to recovery.

This goal does not seem permanently out of reach. There are several steps toward it which are always worth considering.

In the first place, possible precipitating causes should be avoided when possible. A search should be made for focal infections. The patient should be protected against over-exertion and accidents, as far as possible. Female patients should avoid pregnancy.

In the second place, advantage should be taken of the regional differences in incidence of the disorder when circumstances permit. Life in a warm, dry climate seems to have a beneficial effect on many cases—possibly because the common infections of the nose and throat are less prevalent there. Unfortunately, this form of treatment is out of the reach of most patients.

In the third place, a constant search should be made for means of correcting the instability of the plasma. The use of anticoagulants naturally suggests itself; and actually they can be shown to have an effect on some experimental forms of the disease.[22] None of the anticoagulants given by vein (for example, heparin) seem promising. Cysteine is a feeble anticoagulant,[49] which has seemed to afford some protection to some patients. By far the most promising substance seems to be dicoumarin,[50] and it is now being tried on a series of cases.

Meanwhile, symptomatic treatment should not be forgotten. The patient's health and strength must be maintained in every possible way. If spasticity is annoying, small doses of bromides are sometimes useful. Alcohol in moderation may help the patient's spirits, and paradoxically, his balance if ataxia and tremor are present. The use of sandalwood oil and of tincture of belladonna is often helpful in cases of urgency. An important point is that the urgency will often pass off if the patient makes up his mind to disregard it or distracts his attention to some other task. In cases in which the bladder disturbances are of long standing or accompanied by infection, periods of tidal irrigation[51] are often extremely helpful. Patients with hemiataxia may learn to avoid staggering by habitually leaning toward the more normal side. The disagreeable

sensation of slapping the ground with the toes which is a common component of the spastic gait may often be mitigated by practice in placing the heel on the ground first, then rolling the weight along the outer edge of the foot to the toe. A brace may be worn for toe-drop. Subarachnoid alcohol injection or root section may be needed for radicular pains or for contractures in bedridden patients. The foot placement exercises so useful in tabes, are often of benefit in multiple sclerosis also. Special telescopic lenses are available for patients whose loss of vision is relatively fixed and constitutes the most disabling symptom. Motorized wheel chairs may be of use for those unable to walk.

Conclusion

Multiple sclerosis is often regarded as a "rare and mysterious disease." It is certainly not rare, and it is much less mysterious than it once was. A careful, patient analysis of the remaining problems, step by step, gives promise of revealing the roots of the disorder. Even with what we know already, the directions which a rational system of treatment should take is already fairly clear.

REFERENCES

1. Putnam, T. J. The centenary of multiple sclerosis, *Arch. Neurol. & Psychiat.*, 1938, *40:*806.
2. Carswell, R. *Pathological anatomy. Illustrations of the elementary forms of disease.* London, Longman [et al.], 1838.
3. Cruveilhier, J. *Anatomie pathologique du corps humain, ou descriptions avec figures lithographiées at coloriées, des diverses altérations morbides dont le corps humain est susceptible.* Paris, J. B. Baillière, 1942, v. *2.*
4. Charcot, J. M. Histologie de la sclérose en plaques. *Gaz. d. hôp.*, 1868, *41:*554; 557; 566.
5. Charcot, J. M. Diagnostic des formes frustes de la sclérose en plaques, *Progrès méd.*, 1879, *7:*97.
6. Bing, R. and Reese, H. Die multiple Sklerose in der Nordwestschweiz, *Schweiz. med. Wchnschr.*, 1926, *7:*30.
7. Brown, M. R. and Putnam, T. J. Remissions in multiple sclerosis, *Arch. Neurol. & Psychiat.*, 1939, *41:*913.
8. Marburg, O. Allgemeine Pathologie der nichteitrigen Entzündungen des Zentralnervensystems, *Arb. a. d. neurol. Inst. a. d. Wien. Univ.*, 1932, *34:*1.
9. Ferraro, A. Primary demyelinating processes of the central nervous system; an attempt at unification and classification, *Arch. Neurol. & Psychiat.*, 1937, *37:*1100.
10. Juba, A. Die Beziehungen zwischen multipler Sklerose und Encephalomyelitis disseminata, *Deutsche Ztschr. f. Nervenh.*, 1937. *143:*268.
11. Putnam, T. J. Studies in multiple sclerosis, similarities between some forms of "encephalomyelitis" and multiple sclerosis, *Arch. Neurol. & Psychiat.*, 1936, *35:*1289.
12. Putnam, T. J., and Forster, F. "Neuromyelitis optica," a subvariety of multiple sclerosis, *Arch. Neurol. & Psychiat., in press.*
13. Finley, K. H. Pathogenesis of encephalitis occurring with vaccination, variola and measles, *Arch. Neurol. & Psy-*

chiat., 1938, *39:*1047.

14. Adler, H. One hundred cases of a condition diagnosed as encephalitis; clinicopathologic study, *Arch. Neurol. & Psychiat.*, 1940, *44:*541.
15. Joachimovits, R. and Wilder, J. Störungen im Bereiche des weiblichen Genitals bei multipler Sklerose, *Wien. med. Wchnschr.*, 1925, *75:*1331.
16. Beck, R. Multiple Sklerose, Schwangerschaft and Geburt, *Deutsche Ztschr. f. Nervenh.*, 1913, *46:*127.
17. Gayle, R. F., Jr., and Bowen, R. A. Acute ascending myelitis following the administration of typhoid vaccine: report of a case with necropsy findings, *J. Nerv. & Ment. Dis.*, 1933, *78:*221.
18. Wilson, S. A. K. *Neurology.* Baltimore, Williams & Wilkins, 1940, v. *1,* p. 166.
19. de Massary, E. and Mevel, Y. Sérothérapie antitétanique; troubles parétiques; encéphalite léthargique; sclérose en plaques, *Rev. neurol.*, 1921, *1:*347.
20. Putnam, T. J., McKenna, J. B. and Evans, J. Experimental multiple sclerosis in dogs from injection of tetanus toxin, *J. f. Psychol. und Neurol.*, 1932, *44:*460.
21. Globus, J. H. and Bender, M. B. Disseminated toxic degenerative encephalopathy (disseminated sclerosing demyelination) secondary to extensive and severe burns. *J. Nerv. & Ment. Dis.*, 1936, *83:*518.
22. Hoefer, P. F. A., Putnam, T. J. and Gray, M. G. Experimental "encephalitis" produced by injection of various coagulants, *Arch. Neurol. & Psychiat.*, 1938, *39:*799.
23. Fisher, J. H. Encephalomyelitis following administration of sulphanilamide, *Lancet,* 1939, *2:*301.
24. Hilpert, P. Kohlenoxydvergiftung und multiple Sklerose, *Arch. f. Psychiat.*, 1929-30, *89:*117.
25. Ferraro, A. Experimental toxic encephalomyelopathy, *Pyschiat. Quart.*, 1933, *7:*267.
26. Cone, W., Russell, C. and Harwood, R. Y. Lead as a possible cause of multiple sclerosis, *Arch. Neurol. & Psychiat.* 1934, *31:*236.
27. Ecker, A. D. and Kernohan, J. W. Arsenic as a possible cause of subacute encephalomyelitis, *Arch. Neurol. & Psychiat.*, 1941, *45:*24.
28. von Hoesslin, R. *Über multiple Sklerose; exogene Ätiologie, Pathogenese und Verlauf.* Munich. J. F. Lehmann, 1934.
29. Brickner, R. M. and Brill, N. G. Dietetic and related studies on multiple sclerosis, *Arch. Neurol. & Psychiat.*, 1941, *46:*16.
30. Targowla, R. Sclérose en plaques fruste à début mental, *Encéphale,* 1927, *22:* 169.
31. Wilson, S. A. K. and MacBride, H. J. Epilepsy as a symptom of disseminated sclerosis, *J. Neurol. & Psychopath.*, 1925-26, *6:*91.
32. Nielsen, J. M., Wilson, D. C. and Dieterle, R. R. Pyramidopallidal degeneration syndrome due to multiple sclerosis, *Arch. Neurol. & Psychia.*, 1929, *22:* 45.
33. Parker, H. L. Trigeminal neuralgic pain associated with multiple sclerosis, *Brain,* 1928, *51:*46.
34. Davison, C., Goodhart, P. and Lander, J. Multiple sclerosis and amyotrophies, *Arch. Neurol. & Psychiat.*, 1934, *31:* 270.
35. Brickner, R. M. Oscillopsia, a new symptom commonly occurring in multiple sclerosis, *Arch. Neurol. & Psychiat.*, 1936, *36:*586.
36. Marburg, O. Multiple Skleroses, in *Handbuch der Neurologie* (Bunke and Foerster), Berlin, Springer, 1936, v. *13,* pp. 546-693.
37. Adler, A. One hundred cases of a condition diagnosed as acute encephalitis, *Arch. Neurol. & Psychiat.*, 1940, *44:*541.
38. Merritt, H. H. The cerebrospinal fluid in multiple sclerosis, *Brain,* 1934, *57:* 56.
39. Thums, K. Die Ergebnisse der Zwillings-Forschung bei multipler Sklerose, *Nervenarzt,* 1939, *12:*463.
40. Putnam, T. J. Criteria of effective treatment in multiple sclerosis, *J. A. M. A.*, 1939, *112:*2488.
41. Putnam, T. J. and Alexander, L. Disseminated encephalomyelitis; a histologic syndrome associated with throm-

bosis of small cerebral vessels, *Arch. Neurol. & Psychiat.*, 1939, *41:*1087.

42. Collins, J. and Noguchi, H. An experimental study of multiple sclerosis, *J. A. M. A.*, 1923, *81:*2109.
43. Schaltenbrand, G. Nachweis eines Virus als Ursache des uebertragbaren Markscheidenschwundes, *Klin. Wchnschrft.*, 1940, *19:*840.
44. Putnam, T. J. Evidences of vascular occlusion in multiple sclerosis and "encephalomyelitis," *Arch. Neurol. & Psychiat.*, 1937, *37:*1298.
45. Putnam, T. J. Studies in multiple sclerosis; "encephalitis" and sclerotic plaques produced by venular obstruction, *Arch. Neurol. & Psychiat.*, 1935, *33:*929.
46. Simon, B. and Solomon, P. Multiple sclerosis; effect of typhoid vaccine and of epinephrine on coagulation of blood, *Arch. Neurol. & Psychiat.*, 1935, *34:*1286.
47. Simon, B. Blood coagulation in disseminated sclerosis and other diseases of brain stem and cord, *Arch. Neurol. & Psychiat.*, 1942, *48:*509.
48. Putnam, T. J. and Alexander, L. On loss of axis cylinders in sclerotic plaques and similar lesions, *Arch. Neurol. & Psychiat., in press.*
49. Putnam, T. J. and Hoefer, P. F. A. Cysteine hydrochloride as an anticoagulant for clinical use, *Am. J. M. Sc.*, 1939, *198:*502.
50. Wright, I. S. Thrombophlebitis, *Bull. New York Acad. Med.*, 1941, *17:*348.
51. Munro, D. Treatment of urinary bladder in cases with injury of the spinal cord, *Am. J. Surg.*, 1937, *38:*120.